Zagazig University Medical Journal
www.zumj.journals.ekb.eg

ORIGINAL ARTICLE

Is The Combination of Glasgow Coma Scale and Transcranial Doppler Pulsatility Index Improving The Prediction of Outcome in Traumatic Brain Injury Patients?

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ABSTRACT

Background: Glasgow coma scale (GCS) is a familiar scoring system with a standard statistical association with neurological outcome, it has many limitations that minimize its ability in prediction of Traumatic brain injury (TBI) patients' outcome. Transcranial Doppler (TCD) is a noninvasive aid in this field that can improve outcome prediction.

Objective: This study aims to explore the effect of combination of GCS and Pulsatility Index (PI) in the prediction of outcome of TBI patients.

Patients and Method: This study was performed in Zagazig University Hospital (ZUH). 103 traumatic brain injured patients were engaged in the investigations with hospital days of 1, 2, 3, and 7 or until patient discharge. The study was performed by TCD along with GCS recordings. Prognosis was also assessed by the Glasgow outcome scale (GOS).

Results: The sensitivity and negative predictive value of PI was more than GCS in TBI patients (GCS 3-15), as they were (67.5% versus 50%) and (81.1% versus 74.3%), respectively. The combination of both PI and GCS increased the sensitivity and the negative predictive value up to 70% and 83.3%, respectively. PI had higher sensitivity, positive and negative predictive values than GCS in the identification of secondary neurologic deterioration (SND) in mild and moderate TBI patients (73.3% versus 40.0%, 61.1% versus 50.0%, and 92.0% versus 83.9%, respectively), while the combined value of both PI and GCS increased both sensitivity and positive predictive value up to 76.7% and 66.7%, respectively.

Conclusion: The combination of GCS and PI would improve the prediction of outcome.

Keywords: Transcranial Doppler; Traumatic brain injury; Pulsatility Index; Glasco coma scale.

INTRODUCTION

Traumatic brain injury (TBI) is a common cause of mortality and disability worldwide. Outcome of TBI is affected by two varied reasons. They are; the initial insult happening at the onset of trauma and the secondary insult, which consists of the sequential detrimental processes started at the time of trauma with late clinical presentation [1]. Secondary neurological insult increased the load on the susceptible brain even if it was lasting for a few minutes. Therefore, early recognition of those patients and prompt management is of a great importance to improve their outcome. Clinical measures such as Glasgow coma scale (GCS) and pupil size

fail to predict those patients of high risk for worsening. Furthermore, computed tomography (CT) scan had fair association with secondary brain insult in mild and moderate TBI [2]. Moreover, high-quality evidence confirmed that CT scan was not valuable for the prediction of functional recovery in TBI, as the absence of abnormalities on CT at admission did not exclude the occurrence of raised intracranial pressure (ICP), besides significant new lesions may develop in 40% of patients [3]. The weak predictive value of CT for bad outcome in patients with normal initial CT was attributed to the low sensitivity of CT scanning for diffuse axonal injury and diffuse vascular injury [1]. Furthermore, impending risk of cerebral vasospasm or hypoperfusion cannot be predicted by imaging modalities such as CT and Magnetic resonance imaging (MRI) [4] .

GCS consists of three components; verbal, eye, and motor components. GCS had a shortage in evaluation of brainstem reflexes that determine the brainstem arousal activity. Matis and Birbilis, [5] introduced many other limitations disturbing accurate evaluation of all components of GCS and results in inappropriate estimation of conscious level by the GCS.

The GCS was frequently employed in combination with Glasco outcome scale (GOS) in order to assess the relationship between severity of TBI and long-term functional recovery [6,7] GOS was assessed at 28th day from admission. The GOS scores: 4 and 5 were considered as a good outcome, which referred to the independent patients (moderate disability / good recovery). Moderate disability (score 4) signifies the independent but disabled patients where employment is possible, but may special equipment are required. Good recovery (score 5) means recovered patients but may have mild residual effects as minor neurological and physiological deficits. The GOS scores: 1, 2 and 3 were considered as a bad outcome which defined the dependent patients and death (death/vegetative state/severe disability). Vegetative state referred to severe damage with prolonged state of unresponsiveness and a lack of higher mental function. Severe disability referred to conscious but dependent patients [8-10] .

Secondary neurological deterioration (SND) is considered if one of the following objective criteria has occurred [11]: (1) a decrease in GCS of greater than 2 points from the initial GCS in absence of sedative drugs effect; (2) a worsening in neurologic state justifies interference, (e.g., mechanical ventilation, sedation, osmotherapy, transfer to the intensive care unit (ICU), or neurosurgical intervention), [12] and (3) subsequent ICP increase to > 20 mm hg for >10 minutes in mechanically ventilated patients with initial ICP monitoring [2,13] .

Transcranial Doppler (TCD) is a portable device that uses a handheld 2MHz transducer placed above the zygomatic arch in front the tragus of the ear to measure the cerebral blood flow velocity (CBFV) in (cm/s) and PI within the middle cerebral artery (MCA) [14,15] . Due to noninvasiveness of TCD examinations, its importance appeared in the very early phase, as well as during the assessment of patients with cerebral ischemia due to Vasospasms in the setting of subarachnoid hemorrhage. TCD can also be utilized with clinical examination in the verification of brain death [16].

Recent TCD comprised the employment of spectral and color doppler along with grey-scale tissue imaging that allows direct visualization of the major intracranial arteries, allowing identification of arteries and their flow-velocity dynamics [17]. The distinctive criterion of PI value is being a ratio and is not influenced by the angle of insonation, in addition to the strong association between PI and ICP. Thus, PI can be used in non-invasive ICP assessment in the ICU [18], for example, when placing an invasive- ICP monitor is contraindicated (e.g. in severe coagulopathy), where ICP monitoring is not accessible as in equipment's-poor ICU, or in patients with mild to moderate TBI who are without ICP monitor but may be at risk of impending worsening [19].

Reviewing the available literature and keeping in mind the limitations of GCS and threshold of TCD in outcome prediction of TBI, the present study was initiated to investigate the effect of combined GCS and PI in prediction of mild, moderate and sever TBI patients' outcome.

PATIENTS AND METHOD

Sample size

Keeping in mind the previous investigations, sample size was proposed as follows:

PI in patients with no secondary neurological deterioration (SND) was 1.02 (0.66- 1.83) and PI in patients with SND was 1.47(1.07-2.33). At 80% power and 95% CI (confidence interval), the estimated sample size was 103 patients (open EPI).

The Ethical Approval was obtained from the Institutional Review Board (IRB) in Zagazig University (Nb:2471) as the study was performed in Zagazig University Hospitals (ZUH).

Patients and/or their relatives were informed and had the opportunity to refuse their contribution in the study and written informed consent was obtained from all participants and/or their relatives

Moreover, the required measurements are within the protocol of a regular monitoring and follow-up of patients in ICUs of ZUH. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Study design:

103 TBI patients in ZUH were involved in this study over a period of one year, 2016. Patients aged form 18 years to less than 60 years. The head injured patients were divided into two groups: group (1), included mild and moderate TBI patients; and group (2) included sever TBI patients ,where the mild TBI involves (GCS of 14 to 15) and moderate TBI involves (GCS of 9 to 13) and sever TBI involves (GCS of 8 to 3). All patients were assessed by employing TCD on middle cerebral artery; this is along with GCS recordings on hospital days 1, 2, 3 and 7 or until patient discharge. SND is considered as **primary outcome** which assessed at 7^{th} day of admission. SND was diagnosed by one or more of the following objective criteria: (a) A decrease in GCS score of 2 points or more from the initial GCS score without sedative therapy; (b) A deterioration in neurological status sufficient to warrant medical or neurosurgical interventions.

Secondary outcome evaluated by the GOS at 28^{th} day from admission. GOS (4, 5) were considered as good outcome (moderate disability or good recovery).

Whereas bad outcome (death, vegetative state, or severe disability) included GOS (1, 2 and 3).

TCD measurements were performed within the first 8 hours post-TBI employing a Color Doppler-Ultrasound equipment (Siemens Acuson X300 Ultrasound Machine), with P 4-2 phased array 2MHz probe. For all patients, both middle cerebral arteries were insonated through the transtemporal window over zygomatic arch in front of the tragus of the ear at a depth of 50 to 60 mm. Tracings were also recorded for at least 10 cardiac cycles in patients showed stable hemodynamic conditions according to the technique described by Aaslid et al.[15] The highest reading of the two cerebral arteries was selected and the Pulsatility Index (PI) [*Peak systolic velocity (FVS) - End diastolic velocity (FVd) / Time-averaged mean blood flow velocity (FVm)*] was then computed.

The collected data included GCS of 1^{st}, 2^{nd}, 3^{rd}, and 7^{th} days of admission, ICU admission, length of ICU stay, Peak systolic (Vs), end-diastolic (FVd) and time-averaged mean (FVm) velocities and PI of 1^{st}, 2^{nd},3^{rd}, and 7^{th} days of admission.

Exclusion criteria

The exclusion criteria were including patients with clinically significant organ dysfunction on admission, and/or other associated injuries causing hemodynamic instability or patients on high dose vasopressors or inotropes.

STATISTICAL ANALYSIS

Qualitative data were represented as numbers and percentages, while quantitative ones were represented by mean and standard deviation (SD). Chi square test (X^2), *t*-test or Mann Whitney test were applied. Correlation by

Pearson's correlation or Spearman's were also employed. The GCS and the performance of the TCD were assessed according to measurements by cut-off, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) thresholds. To determine spectrum effect, a diagnostic performance of TCD and GCS were checked in subgroups; minor TBI, moderate TBI and sever TBI, as well as in overall population of TBI. Cut off values of both GCS and PI obtained by a Receiver Operating Characteristic (ROC) analysis.

RESULTS

Demographic data

Most of the patients were male that represented 80.6%, The age range was from 18 - to 59 years and the (mean± SD) were (30.39±12.42) years in all patients. While in group 1 and in group 2, the (mean± SD) were (29.41±12.35) years and (31.43±12.72) years, respectively.

Categories of patients

Out of 103 TBI patients, (39 patients were in mild subgroup, 29 patients in moderate subgroup and 35 patients in sever subgroup), were evaluated. From all TBI patients; 34 patients (33.01%) had abnormal measurements on TCD (above cutoff values of PI), and 40 patients (38.8%) had poor outcome. In group 1; 15 patients had SND (22.06%) and 19 patients (27.9%) admitted to the ICU. The ICU admission in (group1) was due to either SND or post-operative care, therefore the patients were admitted first to the ward or the operating room before they admitted to ICU. Moreover, some of patients admitted to ICU after the deterioration that occurred at emergency department (ER) within hours of admission during their engagement in the clinical and radiological survey. Mean± SD of ICU stay were (8 ±1.55) and (22 ± 0.96) in group 1 and group 2, respectively.

Moderate and sever subgroups were significantly higher in distribution of TCD abnormality. Regarding bad outcome, sever was significantly higher followed by moderate and then mild subgroup. Length of ICU stay, and mortality were higher in sever followed by moderate and then mild subgroup, as shown in Table (1).

Pulsatility index (PI)

The cutoff values of PI were more than 1.23 and 1.27 in group 1 and group 2, respectively, as obtained from ROC-curve analysis. Where area under curve (AUC) was 0.821, P =0.001, and 95% confidence interval in group 1. In group 2; AUC was 0.761, P =0.001, and it had 95% confidence interval.

There was a significant difference between two groups in PI value at 3rd and 7th days as shown in Table (2).

Glasgow coma scale

The cutoff values for GCS were less than 11 and 6 in group 1 and group 2, respectively, as obtained from ROC-curve analysis, where AUC was 0.751, P =0.002*, and 95% confidence interval in group 1. In group 2, AUC was 0.716, P =0.02*, and it had 95% confidence interval.

At 1st and 2nd days of admission, the GCS was constant in all TBI patients, and then it was decreased significantly at 3rd and 7th days. This descent due to most of readings at 3rd and 7th days were in sever TBI population, as the most of patients in group 1 (especially the mild subgroup) were discharged from the hospital at the 1st and 2nd days of admission.

Also, there was a significant difference between group 1 and group 2 from 1st till 7th readings, table (2).

Outcome

The first and second readings of PI were significantly higher in bad outcome. GCS was significantly lower throughout the four readings in bad outcome. The distribution of PI and GCS are illustrated in Table (3).

Correlation between PI and GOS

Significant negative correlation between PI and GOS in group 1 was observed with the first three readings. Whereas in group 2, only the first two readings were significant, Table (4).

Correlation between GCS and GOS

A significant positive correlation was noticed between GCS and GOS in group 1with the first two readings. Significant positive correlation

was also found in group 2 with first reading only, Table (4).

Sensitivity, specificity, PPV, NPV

PI has more sensitivity and specificity in group 1 than group 2. GCS was also more sensitive in moderate TBI patients than sever.

In mild TBI, GCS is not valid in the current study, as no patient was found below cutoff value (less than 11).

Comparison between PI with GCS in different subgroups indicated that in sever TBI, PI was more sensitive and had more NPV than GCS. In moderate TBI, PI had more sensitivity, specificity, and NPV than GCS. In mild subgroup the comparison is not valid.

Combined values of PI and GCS revealed that in sever and moderate TBI, sensitivity was the only increased parameter by this combination. In mild TBI subgroup, the combination of PI and GCS had no added value, as the GCS was not valid as previously mentioned, (Table 6). For all TBI patients, the combination of PI and GCS increased both the sensitivity and NPV, Table (5).

Sensitivity, specificity, PPV, NPV in SND

Poor predictive values of GCS were observed in identification of Secondary Neurologic deterioration. While Pulsatility index provided a better predictive value. Combined values of Pulsatility index and GCS showed higher sensitivity and PPV, Table (6).

Table (1): Distribution of TCD abnormality, outcome, length of ICU stays and mortality at 28th day among grades

			Subgroups			Total	X^2	P
			Mild	**Moderate**	**Sever**			
PI	Normal	**N**	**33**	**17**	**19**	**69**	**11.71**	**0.003****
		%	**84.62%**	**58.62%**	**54.29%**	**66.99%**		
	Abnormal	**N**	**6**	**12**	**16**	**34**		
		%	**15.38%**	**41.38%**	**45.71%**	**33.01%**		
Total		**N**	**39**	**29**	**35**	**103**		
		%	**100.00%**	**100.00%**	**100.00%**	**100.00%**		
Outcome	Good	**N**	**34**	**18**	**11**	**63**	**24.15**	**0.00****
		%	**87.20%**	**62.10%**	**31.40%**	**61.20%**		
	Bad	**N**	**5**	**11**	**24**	**40**		
		%	**12.80%**	**37.90%**	**68.60%**	**38.80%**		
Total		**N**	**39**	**29**	**35**	**103**		
		%	**100.00%**	**100.00%**	**100.00%**	**100.00%**		
ICU Stay	Admission	**N**	**5**	**14**	**35**	**54**		
		%	**12.82%**	**48.27%**	**100.00%**	**52.34%**		
	Days mean (range)		**7 (5-9)**	**9 (7-11)**	**22 (14-35)**	**-**		
Total		**N**	**39**	**29**	**35**	**103**		
Mortality	Survived	**N**	**39**	**27**	**31**	**97**	**4.47**	**0.107**
		%	**100.00%**	**93.10%**	**88.60%**	**94.20%**		
	Died	**N**	**0**	**2**	**4**	**6**		
		%	**0.00%**	**6.90%**	**11.40%**	**5.80%**		
Total		**N**	**39**	**29**	**35**	**103**		
		%	**100.00%**	**100.00%**	**100.00%**	**100.00%**		

*** P is significant at the 0.01 level, * P is significant at the 0.05 level, and X^2 is Chi-squared test.*

Table (2): PI and GCS values distribution for all TBI patients, in groups 1 and 2

PI distribution	**Group 1** (N=68)	**Group 2** (N=35)	**P- value**
	Mean± SD	**Mean± SD**	**p**
PI_1	1.12±0.24	1.20±0.42	0.219
PI_2	1.09±0.18	1.10±0.46	0.416
PI_3	1.04±0.21	0.90±0.25	0.002**
PI_7	1.01±0.11	0.87±0.18	0.04**
GCS distribution	**Mean± SD**	**Mean± SD**	**p**
GCS_1	12.82±2.10	5.91±1.40	0.001 **
GCS _2	12.53±2.69	6.17±1.87	0.001 **
GCS _3	10.0±3.53	5.74±2.02	0.001 **
GCS _7	11.75±2.18	6.96±2.66	0.001 **

*** P is highly significant at the 0.01 level, * P is significant at the 0.05 level, t-test*

Table (3): PI and GCS distribution between good and bad outcome (in group 1 and group 2)

Groups		**PI_1**		**PI_2**		**PI_3**		**PI_7**	
	outcome	Bad outcome	Good outcome	Bad outcome	Good outcome	Bad outcome	Good outcome	Bad outcome	Good outcome
Group 1	Mean±SD	1.363±0.25	1.04±0.18	1.14±0.21	1.01±0.16	1.16±0.26	1.02±0.12	1.14±0.14	1.08±0.00
	t- test	5.214		2.387		1.412		0.083	
	P	0.00**		0.02*		0.162		0.981	
Group 2	Mean±SD	1.289±0.37	1.02±0.28	1.21±0.41	0.88±0.16	0.95±0.28	0.87±0.18	0.89±0.19	0.86±0.14
	t- test	2.077		2.214		0.616		0.281	
	P	0.046*		0.021*		0.514		0.78	
Group 1		**GCS_1**		**GCS_2**		**GCS_3**		**GCS_7**	
	Mean±SD	10.0±1.87	13.45±1.58	9.25±2.09	13.36±2.13	8.07±2.7	11.66±2.87	9.8±1.3	13.14±1.46
	t/Mann Whitney	-6.828		-5.986		-3.078		-4.072	
	P	0.001**		0.001**		0.005**		0.002**	
Group 2	Mean±SD	5.33±1.12	7.36±0.8	5.47±1.67	7.5±1.5	4.86±1.62	7.6±1.43	6.14±2.3	10.0±3.25
	t/Mann Whitney	-5.348		-3.193		-4.563		-3.515	
	P	0.001**		0.004**		0.001**		0.001**	

*** P is significant at the 0.01 level, * P is significant at the 0.05 level, and t/ Mann Whitney: T test / Mann Whitney test*

Table (4): Correlations between GOS and (PI , GCS) (in groups 1 and 2)

Groups	PI_1		PI_2		PI_3		PI_7	
	r	P	r	P	r	P	r	P
Group 1	-0.353	0.003**	-0.276	0.033*	-0.510	0.008**	-0.082	0.948
Group 2	-0.504	0.002**	-0.576	0.001**	-0.275	0.110	-0.052	0.767
	GCS_1		GCS_2		GCS_3		GCS_7	
	r	P	r	P	r	P	r	P
Group 1	0.643	0.001**	0.538	0.001**	0.158	0.571	0.144	0.621
Group 2	0.447	0.021*	0.103	0.458	0.149	0.421	0.135	0.441

*** Correlation is significant at the 0.01 level, and * Correlation is significant at the 0.05 level.*

Table (5): Validity of PI, GCS, and combined PI and GCS value in detection of TBI outcome in different subgroups (mild, moderate, and sever) and in overall TBI patients

	Sensitivity	Specificity	+VE predictive	-VE predictive	Accuracy
PI in mild	80.0%	94.1%	66.7%	96.9%	92.3%
PI in moderate	81.8%	83.3%	75.0%	88.2%	82.7%
PI in sever	58.3%	81.8%	87.5%	47.3%	65.7%
GCS in mild	NA	100.0%	NA	87.1%	87.1%
GCS in moderate	72.7%	77.8%	66.7%	82.3%	75.8%
GCS in sever	50.0%	90.9%	92.3%	45.4%	88.8%
PI & GCS in mild	80.0%	94.1%	66.7%	96.9%	92.3%
PI & GCS in moderate	83.3%	79.0%	75.0%	83.3%	80.7%
PI & GCS in sever	60.5%	87.0%	90.9%	45.5%	73.3%
PI in all patients	67.5%	88.9%	79.4%	81.1%	80.5%
GCS in all patients	50.0%	92.1%	80.0%	74.3%	75.7%
PI & GCS in all patients	70.0%	90.4%	73.6%	83.3%	83.3%

Table (6): Validity of PI, GCS and combined PI and GCS in detection of SND in group (1)

	Sensitivity	Specificity	+VE predictive	-VE predictive	Accuracy
PI	73.3%	86.8%	61.1%	92.0%	83.8%
GCS	40.0%	88.7%	50.0%	83.9%	77.9%
PI & GCS	76.7%	83.3%	66.7%	83.3%	85.2%

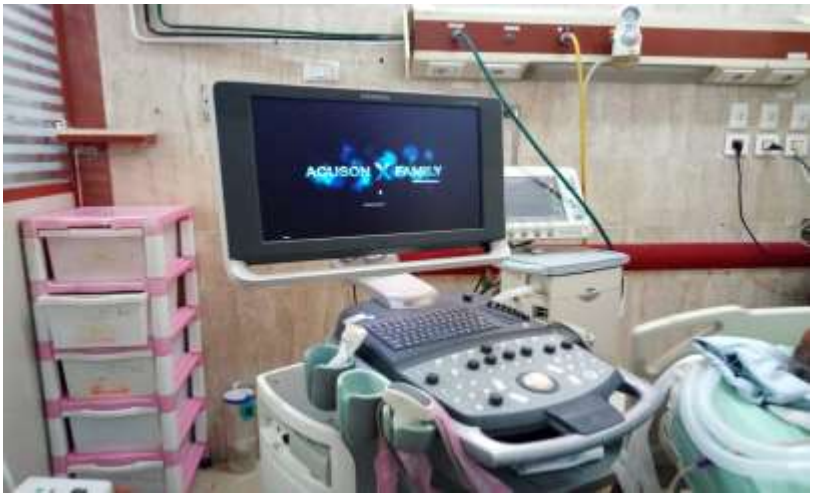

Figure 1. Siemens Acuson X300 Ultrasound Machine

DISCUSSION

Throughout this study, the group 1 showed that NPV of PI was higher than its PPV (92.0%, and 60.1%, respectively), this revealed that normal TCD pattern was more indicative of predicting outcome than abnormal pattern and these results agreed with the results of Bouzat et al. [2].The Bouzat's results showed low value of PPV (18%), however our results have a higher PPV of 60.1%. This is attributed to the considered exclusion of criteria that can increase PI, such as aortic regurge and old patients (≥60 years). Other reasons were the bad outcome in their study was lower than our study (10.2% versus 23.5%) which may indicate the inadequate medical services supply as a result of traffic delay and/or low availability of the specialist hospitals.

our results showed that PI was less sensitive in sever TBI patients (group 2), Jaffres et al. [12] stated that FVm was more sensitive in those patients, and they recommended further studies to define the most sensitive TCD parameter in mild and moderate TBI, [20].

Cutoff value of PI in group 2 was greater than those of group 1, (1.27 versus 1.23), This is due to more severity of brain lesions and use of mechanical ventilation in sever TBI patients [2,13]. The present study supported the conclusions of (Trabold et al. [21]; Prasad et al. [4]), as they concluded the cutoff value of PI on sever TBI as more than 1.3 and 1.4, respectively. Tan et al. [22] performed TCD on 96 adult patients with severe TBI and an ICP monitor in place. They concluded that a FVm of less than 40 cm/s and a PI of greater than 1.5 within 24 hours of admission were associated with a high ICP and a poor outcome.

Out of 68 patients in group 1, 15 patients had SND (22.06%). Jaffres et al. [12] and Bouzat et al. [13] concluded a close value of SND (21.7% and 21% respectively). While the study of Bouzat et al. [2] in 2016 presented a surprising value of SND which was 6%, they believed that this value was due to the special medical care was provided for patients with abnormal TCD readings on admission.

A significant association between PI values and patient outcome was confirmed here in this study that agreed with Prasad et al. [4] who concluded that the high PI values are correlated with unfavorable neurological outcome.

Significant positive correlation was established between GCS and GOS in group 1 and group 2. These results agreed with many other literatures [23-26].On the other side, Balestreri et al. [27] and Matis and Birbilis [28] determined no correlation between GCS and Glasgow outcome scale (GOS), this is attributed to the limitations affecting their studies such as being a retrospective study on relatively small sample size (60 patients), the great frequency of the GCS score of 3, and the identification of outcome only as survival or death.

It is worthy to mention that the GCS in group 2 showed obviously low sensitivity (50%), this

may be due to sedated and mechanically ventilated patients who lead to underestimation of GCS, and this result agreed with investigations of Marion and Carlier, [29]. They analyze the difficulty of determining the initial GCS in a repeatable and reproducible manner and identify more aggressive prehospital treatment, involving early sedation and intubation, as a factor obscuring the real GCS assessment

CONCLUSIONS

The current study indicated that the combination of GCS and PI may be used as a tool for improving the prognosis of all patients with TBI. This is attributed to the increase in sensitivity and NPV thresholds by the combination of these two predictors rather than a single one.

Important role of the PI in prediction of SND was appeared throughout our study which relatively can compensate the poor predictive value of GCS in SND prediction.

So, we recommend further studies to assess GOS for more extended periods with larger sample size.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding information

None declared

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To cite this article: Abdelhaleem NF, Othman HA, Abdel Razek GM, Soliman AHS, Abdel Galel EF. Is The Combination of Glasgow Coma Scale and Transcranial Doppler Pulsatility Index Improving The Prediction of Outcome in Traumatic Brain Injury Patients? ZUMJ 2019;25(5);529-538,DOI: 10.21608/zumj.2019.10082.10740.